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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,379	09/27/2004	Shogo Ishiuchi	Q83588	5052

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WASHINGTON, DC 20037-3213

EXAMINER	
MAEWALL, SNIGDHA	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
06/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,379	ISHIUCHI, SHOGO	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-12,14-17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

1. Receipt of Applicant's arguments/remarks and amended claims filed on 03/20/09 is acknowledged.

Restriction/Election

Applicant's had elected without traverse of Group IV, claims 13-16 and the elected compound "7-acetyl-5-(4-aminophenyl)-8(R)-methyl-8,9-dihydro-7H-1,3-dioxolo [4,5-h] [2,3]benzodiazepine (Talampanel) in the reply filed on 08/01/08 is acknowledged.

Claims 1-12 and 14-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 08/01/08.

Newly submitted claim 19 is directed to multiple compounds which were not elected in the original presentation.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 19 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 13 and 18 read on the elected species. Claim 13 being generic claim.

Claims 14-17 are non elected species and were inadvertently included in prosecution.

Claims **13 and 18** are under prosecution as per the original election of species requirement and response filed on 08/01/08.. The election of species was without traverse. The restriction is deemed final.

Claims **13 and 18** are under prosecution.

The rejections not reiterated herein have been withdrawn in view of Applicant's arguments.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 13 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro treatment of glioblastoma does not reasonably provide enablement for in vivo treatment of glioblastoma with each and every compound claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

A method for treating glioblastoma comprising administering a therapeutically effective amount of a compound having an activity of inhibiting an alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor to a patient with the disease.

The invention relates to method of treating glioblastoma comprising administering a therapeutically effective amount of a compound (claim 13) having an activity of inhibiting an alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor to a patient with the disease. The specification does not provide in-vivo correlation of each and every kind of AMPA antagonist in treating glioblatoma.

The state of the art as given by Theodora et al. (Clinical Predictive value of the in vivo cell line, human Xenograft, and Mouse Allograft Preclinical Cancer Models) Clinical cancer research 4227, vol. 9, 4227-4239, September 15, 2003). The prior art teaches that in phase II clinical trials, there is growing effort toward validating new endpoints of drug efficacy. The effectiveness of drug will bring new challenges in terms of preclinical predictors of activity, see last paragraph. Hence the state of the art posses unpredictability in in-vivo efficacy of drugs in cancer treatments.

The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art.

2. The breadth of the claim

The scope of the claims does not commensurate with the scope of the

disclosure. The claims are very broad and as recited encompass unlimited compound in treating glioblastoma in vivo.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for compounds which are AMPA antagonist.

[The instant disclosure provides no evidence to suggest that this unique activity can be extended to any compound and thus does not meet the "how to use" prong of 35 USC 112, first paragraph with regard thereto.]

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used without undue experimentation as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Response to Arguments/Declaration

3. Applicant's arguments filed 03/20/09 have been fully considered but they are not persuasive.

Applicants arguments regarding in vitro correlation of AMPA antagonist was persuasive, how ever, new rejection has been made with regard to correlation of in vitro and in vivo results in terms of predictability. The declaration does not provide in vivo correlation of each and every AMPA anatagonist with glioblastoma treatment and unpredictability in the state of the art as stated above does not enable one of ordinary to practice the invention within full scope of the claimed invention.

Declaration

4. The declaration under 37 CFR 1.132 filed 03/20/09 is insufficient to overcome the rejections of claims 13 and 18 based upon the prior art and enablement issues as set forth herein.

The declaration does not provide in-vivo results of any or every or all AMPA antagonist which exists in pharmaceutical art in providing in vivo treatment of glioblastoma. The declaration is not commensurate with the scope of claim.

Claim Rejections - 35 USC § 103

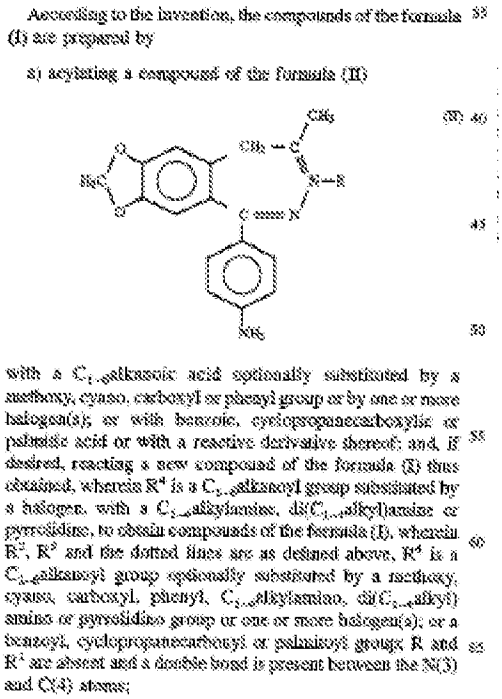
5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable

over in view of Andrasi et al. (USP 5,639,751) in view of Rothstein et al. (Nature medicine, vol. 7, number 9, September 2001, presented in IDS).

Andrasi et al. teach the claimed compound (Talempanel) and the use of such compound in treating various diseases of central nervous system. (Abstract). These compounds have been characterized as having a property of inhibiting AMPA receptors. (See column 3 as depicted below.



According to the invention, the compounds of the formula (I) are prepared by

a) acylating a compound of the formula (II)

(II)

with a C_{1-6}alkanoic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s), or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of the formula (I) thus obtained, wherein R^4 is a C_{2-6}alkanoyl group substituted by a halogen, with a C_{1-6}alkylamine, di(C_{1-6}alkyl)amine or pyrrolidine, to obtain compounds of the formula (I), wherein R^2, R^3 and the dotted lines are as defined above, R^4 is a C_{3-6}alkanoyl group optionally substituted by a methoxy, cyano, carboxyl, phenyl, C_{1-6}alkylamino, di(C_{1-6}alkyl) amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms;

The reference does not correlate AMPA antagonist with treatment of glioblastoma. However, Rothstein et al. disclose that Gliomas are the most common tumors of the central nervous system and have a wide range of properties. Glioblastoma is a highly malignant and fatal brain tumor (see second column, last paragraph and 3rd column, last paragraph). The article discloses that blockade

of the NMDA (N-methyl-D-aspartate) glutamate receptor subtype clearly abrogated the *in situ* growth of tumors in a rat model. Interestingly, the blockade of NMDA and AMPA glutamate receptors has recently been reported to decrease the proliferation of various tumors such as colon, adenocarcinoma, breast, astrocytoma and lung carcinoma, suggesting a direct cytostafic effect, at least *in vitro,* of glutamate blockade see page 995, middle column first paragraph.

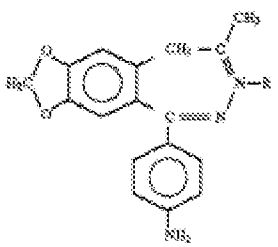
It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the AMPA antagonist as disclosed by Andrasi et al. (which reads on the instant compound) in treating glioblastoma in view of the teachings of Rothstein et al.

7. Claims 13 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrasi et al. (USP 5,639,751) in view of Takano *et al.,(* "Glutamate release promotes growth of malignant giiomas", Nature Medicine, 7 (9), pp. 1010-1015 (2001) presented in IDS) and Catarina L. Florian *et al.,* ("Characteristic metabolic profiles revealed by IH NMR spectroscopy for three types of brain and nervous system tumours", NMR in Biomedicine,Vol. 8, pp. 253-264 (1996) presented in IDS).

Andrasi et al. teach the claimed compound and the use of such compound in treating various diseases of central nervous system. (Abstract). These compounds have been characterized as having a property of inhibiting AMPA receptors. (See column 3 as depicted below.

According to the invention, the compounds of the formula (I) are prepared by

a) acylating a compound of the formula (II)



with a C_{1-6}alkanoic acid optionally substituted by a methoxy, cyano, carboxyl or phenyl group or by one or more halogen(s); or with benzoic, cyclopropanecarboxylic or palmitic acid or with a reactive derivative thereof; and, if desired, reacting a new compound of the formula (I) thus obtained, wherein R^4 is a C_{1-6}alkanoyl group substituted by a halogen, with a C_{1-6}alkylamine, di(C_{1-6}alkyl)amine or pyrrolidine, to obtain compounds of the formula (I), wherein R^2, R^3 and the dotted lines are as defined above, R^4 is a C_{1-6}alkanoyl group optionally substituted by a methoxy, cyano, carboxyl, phenyl, C_{1-6}alkylamino, di(C_{1-6}alkyl) amino or pyrrolidino group or one or more halogen(s); or a benzoyl, cyclopropanecarbonyl or palmitoyl group; R and R^1 are absent and a double bond is present between the N(3) and C(4) atoms;

Andrasi also teaches that talampanel is AMPA receptor antagonist.

Takano discloses the effectiveness of a substance having a glutamate receptor antagonist action (the NMDA receptor antagonist MK801) in suppressing the growth of gliomas, which are glutamate-secreting tumour cells, see the whole article. Florian discloses the fact that glioblastomas secrete glutamate, see the whole article.

As such, it would have been obvious to one of ordinary skill in the art to utilize the compounds taught by Andrasi et. al.. in treating glioblastoma motivated by the teachings of Takano et al. and Florian et al. and arrive at the claimed invention with the reasonable expectation of success.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/
Examiner, Art Unit 1612
/Gollamudi S Kishore/
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